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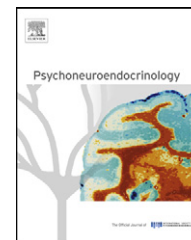
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REVIEW

Adulthood trauma and HPA-axis functioning in healthy subjects and PTSD patients: A meta-analysis

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Trauma;
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Summary

Background: Hypothalamic–pituitary–adrenal (HPA)-axis dysregulation has inconsistently been associated with posttraumatic stress disorder (PTSD). Yet, trauma exposure rather than PTSD may be responsible for HPA-axis dysregulation. In two meta-analyses, we assessed the association of adulthood trauma exposure and HPA-axis functioning in healthy subjects with and without PTSD.

Method: A literature search in Pubmed and PsychInfo, using keywords and MeSH terms such as cortisol, emotional trauma, and PTSD, was performed. Only studies that included mentally healthy trauma-exposed (TE) individuals as well as non-exposed (NE) healthy individuals and/or PTSD patients (PTSD) were selected. This resulted in 1511 studies of which ultimately, 37 studies (21 TE versus NE and 34 TE versus PTSD, $N = 2468$) were included. Methodological quality of all studies was assessed according to specific quality criteria. Pooled effect sizes (Hedges's g) on cortisol levels were compared. For all analyses, random effect models were used.

Results: Cortisol levels were neither significantly different between TE versus NE subjects (-0.029 ; 95%CI: -0.145 ; 0.088) nor between TE subjects versus PTSD patients (0.175 ; 95%CI: -0.012 ; -0.362). Subgroup analyses showed an increased cortisol suppression after the low dose dexamethasone suppression test (DST) in TE versus NE subjects (-0.509 ; 95%CI: -0.871 ; -0.148). This meta-analysis was limited by the fact that lifetime psychiatric illness and childhood trauma were not an exclusion criterion in all 37 studies.

Conclusion: Neither adulthood trauma exposure nor PTSD were associated with differences in HPA-axis functioning, although adulthood trauma may augment cortisol suppression after the DST. More evidence on other dynamic tests of HPA-axis functioning in PTSD and adulthood trauma exposure is needed.

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Introduction

Trauma exposure, often involving a threat to life or the prospect of serious injury, may increase the vulnerability to the development of many psychiatric disorders, which is most evident in posttraumatic stress disorder (PTSD). In patients with PTSD, neurobiological alterations of the HPA-axis have been found. In 1986, Mason et al. were the first to describe low urinary cortisol levels in patients with PTSD. In a subsequent study, the same research group replicated the results (Yehuda et al., 1990). They concluded that these findings suggest a physiological adaptation of the HPA-axis to chronic stress. Since then, many studies on cortisol under basal and challenged conditions in patients with PTSD have reported alterations in hypothalamic–pituitary–adrenal (HPA)-axis functioning in patients with this disorder.

Several techniques are currently in use to assess HPA-axis functioning. Cortisol is secreted with a pulsatory diurnal rhythm, with a peak (average increase of 50%) approximately 30 min after awakening, and a progressive decline during the day. Cortisol levels under basal conditions mainly reflect adrenal functioning, and may be assessed in several bodily fluids such as saliva, blood (serum or plasma) and urine. Several challenge paradigms targeting the HPA-axis at different levels are also used frequently. The low dose dexamethasone suppression test (DST) is the most widely used challenge test in neurobiological stress research. Ingestion of 0.5 mg of dexamethasone at 23.00 h on the night before the test day leads to downregulation of the HPA-axis due to feedback inhibition and induces a modest suppression of the HPA-axis, enabling differentiation between normal, enhanced suppression, and non-suppression. By collecting cortisol samples before and after dexamethasone administration, the feedback effects of dexamethasone on the HPA-axis can be calculated. In psychiatric populations, the DST

was first used in patients with major depressive disorder (MDD), who showed non-suppression of cortisol in response to dexamethasone (Carroll et al., 1976). Enhanced suppression of cortisol is reported in patients with PTSD (Yehuda et al., 1993, 1995a, 2004b) but also in trauma-exposed veterans without PTSD (de Kloet et al., 2007). A potentially more sensitive measure to study negative feedback regulation of the HPA-axis is the combined dexamethasone/corticotropin-releasing hormone (Dex/CRH) test, originally developed by Holsboer et al. (1987). The Dex/CRH has been reported to differentiate between patients with MDD and healthy controls and it has therefore been argued that the Dex/CRH test can unveil more subtle HPA-axis disturbances. Psychological stress challenges, such as the Trier Social Stress Test (TSST) have also been used to study HPA-axis functioning in relation to trauma-exposure. Most studies that used non-pharmacological stress challenges, however, focused on childhood trauma exposure (Heim et al., 2000; Elzinga et al., 2003, 2008; Carpenter et al., 2007), whereas only a few involved adulthood trauma (Liberzon et al., 1999; Bremner et al., 2003).

Since Mason et al. (1986), many studies on cortisol under basal and challenged conditions in patients with PTSD have reported alterations in hypothalamic–pituitary–adrenal (HPA)-axis functioning in patients with this disorder. However, the results are not consistent. Some studies reported lower cortisol levels in PTSD patients compared to a non-clinical sample (Rohleder et al., 2004; Neylan et al., 2005; Yehuda et al., 2005b; Wessa et al., 2006; de Kloet et al., 2007), whereas other studies reported higher cortisol levels in patients with PTSD (Lindley et al., 2004; Inslicht et al., 2006). Interestingly, military veterans with PTSD showed lower levels of cortisol in the first hour after awakening compared to non-trauma-exposed (NE) civilian controls. However, compared to a control group with a history of

deployment related trauma exposure (e.g., being shot at, ambushed or taken hostage, seeing others being killed or injured, and witnessing human suffering during military operations, such as combat or peace-enforcement operations), no differences in cortisol concentrations were reported (de Kloet et al., 2007).

There may be several explanations for the mixed results that have been reported. First, different HPA-axis outcome measures reflect different HPA-axis mechanisms; basal functioning (Rohleder et al., 2004; Golier et al., 2006, 2007; de Kloet et al., 2007; Gill et al., 2008; Klaassens et al., 2010a,b) versus various dynamic tests (Yehuda et al., 2002; de Kloet et al., 2007; Klaassens et al., 2010a,b) of HPA-axis reactivity have been used. Second, different types of trauma (e.g., combat, Holocaust, other) are involved (Yehuda et al., 1995a; Boscarino, 1996; Bonne et al., 2003; Seedat et al., 2003; Griffin et al., 2005; Inslicht et al., 2006; Klaassens et al., 2010a,b). Third, long term effects of early life trauma (or early developmental stage) (Heim et al., 2000; Meinschmidt and Heim, 2005; Carpenter et al., 2007; Tyrka et al., 2008) may have a different effect on HPA-axis function in adult life than trauma exposure during adulthood. Evidence from studies in rodents and non-human primates have shown that maternal separation and other trauma exposures early in life induced persistent changes in the set-point of the HPA-axis in such a way that there is an altered biological and behavioural reactivity to stress in later life; these long-lasting effects seemed stronger than upon trauma exposure during adulthood (Sanchez et al., 2001; Tarullo and Gunnar, 2006).

Finally, in many studies healthy subjects with and without a history of trauma exposure are brought together in a single control group, often without making a distinction between them (Smith et al., 1989; Lecrubier et al., 1997; Yehuda et al., 2004a, 2007; Lindley et al., 2004; Golier et al., 2006). Therefore, the effect, if any, of trauma exposure in the absence of psychopathology on HPA-axis functioning, is currently unclear. The few studies that included separate trauma-exposed (TE) and non-exposed (NE) control groups reported conflicting results. Some studies found HPA-axis alterations after trauma irrespective of the presence of psychopathology (de Kloet et al., 2007; Klaassens et al., 2009, 2010b), whereas other studies reported HPA-axis dysregulation after trauma only in relation to PTSD (Yehuda et al., 2002; Griffin et al., 2005; Wessa et al., 2006).

In this paper, we present meta-analyses of studies on the relationship between adulthood trauma, HPA-axis functioning and PTSD. Because the impact on HPA-axis functioning may be different for adulthood versus childhood trauma exposure, and because many groups of people are at risk for trauma exposure during adulthood (e.g., military personnel, police officers, fire-fighters, rescue workers, health care workers), we focussed on adulthood trauma in non-clinical and PTSD samples. In addition, basal HPA-axis functioning as well as dynamic tests of the HPA-axis were analyzed. We carried out two meta-analyses: in our first meta-analysis we examined the association of trauma exposure during adulthood and HPA-axis functioning in healthy subjects without psychiatric disorders (TE) and compared them with healthy subjects without a history of trauma exposure (NE). In our second meta-analysis we examined whether these trauma-exposed individuals without psychiatric disorders differed

from PTSD patients. Our aim was to establish whether trauma exposure during adulthood is associated with HPA-axis dysregulation in the absence and presence of PTSD.

Methods and materials

First, relevant studies were identified and selected according to specific in- and exclusion criteria. After selection of the studies, methodological quality of the studies was assessed according to eight quality criteria.

Identification of studies

To identify relevant studies published in the English language, a systematic computerized literature search in the databases of PubMed and Psycinfo was performed from the earliest available date up to January 2010. The following (key)words and MeSH terms, including combinations, were used: 'post-traumatic stress disorder', 'PTSD', 'hydrocortisone', 'cortisol', 'dexamethasone', 'HPA-axis', 'life change events', 'psychological stress', 'emotional trauma', 'combat disorders', and 'veterans', with limitations set on 'humans' and 'adults'. In addition, reference lists of the selected articles were checked for further relevant publications, as were reference lists of other relevant meta-analyses and reviews (Burke et al., 2005; Otte et al., 2005; de Kloet et al., 2006; Meewisse et al., 2007; Chida and Steptoe, 2009; Handwerker, 2009). To be selected, studies had to include a group of TE subjects. In addition, the studies had to assess either a group of NE controls, to facilitate comparisons between TE and NE subjects, or a group of PTSD patients in order to facilitate comparisons between TE subjects and PTSD patients. Needless to say, studies that assessed all three groups were included in the meta-analyses as well. Studies that only included PTSD patients and NE subjects were excluded. The selection process consisted of three phases. At first, the inclusion criteria were applied to the citations generated from the searches by the first author (EK). During the next phase, titles identified as potentially relevant, were requested in full text papers and closely read by EK who also made the second selection. In the third phase, all studies that were potentially eligible for the meta-analysis ($n = 150$) were assessed independently by EK, EG and/or TV. In case of inconsistencies on a study, it was openly discussed until consensus was reached.

In- and exclusion criteria

Only published case-control studies on humans exposed to trauma during adulthood, written in the English language were eligible. Studies were included when (a) the design included a TE group as well as a NE group and/or a group of PTSD patients; (b) the HPA-axis outcome measures were either salivary, plasma, or 24-h urinary cortisol; (c) the HPA-axis measurement included either basal assessment, characteristics of the diurnal variation of cortisol, the DST, or reactivity after the Dex/CRH test or a psychological challenge test (Figure 1); (d) mean cortisol levels and standard deviations (SD), standard error (SE) or confidence interval (CI), p -values or other statistics for the groups were described; (e) patients had current PTSD, established with

<p>Basal HPA-axis functioning</p> <ul style="list-style-type: none"> - Salivary cortisol <ul style="list-style-type: none"> - cortisol response to awakening - cortisol diurnal decline - Plasma cortisol <ul style="list-style-type: none"> - single time point - diurnal - Urinary cortisol <ul style="list-style-type: none"> - 24 h urinary cortisol
<p>Dynamic HPA-axis functioning using pharmacological challenges</p> <ul style="list-style-type: none"> - DST <ul style="list-style-type: none"> - dexamethasone suppression test - Dex-CRH challenge <ul style="list-style-type: none"> - dexamethasone corticotropin releasing hormone

Figure 1 Types of HPA-axis functioning tests included in the meta-analyses.

a DSM-based diagnostic interview (studies using merely a measure of symptom severity were not included); (f) at least two studies on the same type of HPA-axis assessment were present; (g) TE and NE subjects were without current psychiatric disorder as assessed with a DSM-III or IV (semi-)structured interview (e.g., Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-I], Mini-International Neuropsychiatric Interview [M.I.N.I.] or Composite International Diagnostic Interview [CIDI]). Two studies (Lauc et al., 2004; Gill et al., 2008) did only assess the absence of current PTSD and MDD, the latter using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). Nonetheless, they were included in the meta-analysis. One of these studies had an overall quality score that was suboptimal (Lauc et al., 2004). In case of studies fulfilling all inclusion criteria and reporting data on overlapping cohorts, the study with the largest sample size was included ($n = 2$) (Yehuda et al., 1995b; Golier et al., 2007). When sample sizes were equal, the study with the most complete information was included ($n = 2$) (Yehuda et al., 1995a; Young and Breslau, 2004). One study (de Kloet et al., 2008) was excluded because it was the only study that used the Dex/CRH test to examine HPA-axis functioning in TE subjects versus PTSD patients.

Exclusion criteria were (a) childhood trauma but not adulthood trauma was assessed; (b) childhood trauma was assessed in addition to adulthood trauma and some individuals only reported childhood trauma; (c) clinically significant adrenocortical and thyroid diseases or any serious unstable medical condition was present; (d) it was unclear whether subjects also suffered from current PTSD.

Quality assessment

Because the HPA-axis is a delicate system that is influenced by many factors, elimination of as many factors that are known to potentially influence HPA-axis regulation, may well improve the quality of studies. In addition, previous studies have shown that the quality of studies may be improved by taking certain

in- and exclusion criteria into account. Assessment of salivary cortisol on several time points and on more than one day is necessary to reliably assess the cortisol rise after awakening (Hellhammer et al., 2007). Studies among recovered depressives have shown that HPA-axis functioning may not return to normal, resulting in so-called 'scarring' (Zobel et al., 2001; Bhagwagar et al., 2003; Appelhof et al., 2006). In PTSD patients who were successfully treated, an increase in plasma cortisol levels was found after controlling for depressive symptoms (Olff et al., 2007). Because PTSD and major depression often co-occur, we have decided to give a quality point to studies that excluded recovered patients in their TE and NE groups. Also, several types of psychotropic medication, especially antidepressants, may affect HPA-axis functioning (Deuschle et al., 1997, 2003; Greden et al., 1983; Holsboer-Trachsler et al., 1991; Mantney et al., 2011). All the factors mentioned above were considered to be factors that improve the methodological quality of studies on HPA-axis functioning.

The quality of the included studies was independently assessed by two authors (EK and EG), using a checklist of 8 criteria. All quality criteria for each study were coded as either positive or negative. A study was considered to be of high quality when at least 5 of the following criteria were positive: (1) HPA-axis reactivity (e.g., Dex/CRH, psychological stress test) was assessed and/or the low dose DST was performed; (2) multiple time points were assessed; (3) basal cortisol was assessed on more than one day for the same outcome measure; (4) either blood samples were collected or, in the case of salivary cortisol sampling, extensive instructions were given or a monitoring device was used; (5) detailed trauma assessment was carried out (6) potentially confounding variables were taken into account; (7) when lifetime psychiatric history as assessed with a DSM-III or IV (semi-)structured interview in both the TE and NE groups was excluded. In case only the absence of current PTSD and MDD was assessed, we decided to include the studies as well ($n = 3$); (8) use of psychotropic medication or other medication that is known to influence HPA-axis functioning was excluded.

If a study did not report whether it met a specific quality criterion it was coded as negative. Disagreements were discussed until consensus was reached.

Data analysis and power calculation

Data management, calculation of effect sizes and calculation of the pooled mean effect sizes were performed using Comprehensive Meta-analysis (version 2.0.021, Biostat, Englewood, NJ, USA).

Two meta-analyses were conducted; one for the TE subjects versus the NE control subjects, and one for the TE subjects versus the PTSD patients. Effect sizes were calculated for three types of outcome data: (1) mean cortisol differences between the study groups (TE vs. NE and TE vs. PTSD), (2) the difference between the study groups percentage cortisol suppression to the DST, and (3) the Area Under the Curve with respect to ground (AUC_g) of the cortisol levels after the Dex/CRH test. The AUC_g is a composite measure calculated according to the trapezoidal method (Pruessner et al., 2003). In the overall meta-analyses, the effect sizes for the DST ($n = 5$ for the TE versus NE groups and $n = 9$ for the

TE versus PTSD patients group) and Dex/CRH test ($n = 2$ for the TE versus NE groups) were analyzed separately, because the interpretation of dynamic tests is different from basal conditions. These outcome measures were assessed in subgroup analyses only. Hedges's g (Hedges, 1982) weighted effect size was used as metric for all mean comparison. Hedges's g adjusts for differences in (small) sample sizes and yields a more conservative metric than Cohen's d (Deeks et al., 2009). All analyses were performed with the random-effects model. To assess heterogeneity between the studies we calculated the I^2 , which is an indicator of heterogeneity in percentages. A zero percent (0%) value means no observed heterogeneity, and higher values represent increasing heterogeneity. Generally heterogeneity is categorised in 25% (low), 50% (moderate) and 75% (high) (Higgins et al., 2003). In addition, Q -statistics were calculated. A statistically significant Q rejects the null hypothesis of homogeneity and indicates a heterogeneous distribution of effect sizes between studies, meaning that systematic differences are present, and may influence the results.

The presence of publication bias was assessed by inspecting the funnel plot on primary outcome measures (effects on cortisol levels) and by Duval and Tweedie's trim and fill procedure (Duval and Tweedie, 2000) as implemented in the CMA software. This procedure yields an estimate of the effect size after publication bias has been taken into account, by calculating adjusted values of the pooled mean effect sizes and 95% confidence intervals. In this procedure, random effects models were used.

Power calculation

As proposed by Lipsey (1990), effect sizes of 0.3 were considered to be small. To investigate if there was sufficient statistical power in our meta-analysis to detect a small effect size, we conducted a power calculation according to the procedures described by Borenstein et al. (2009). These calculations indicated that we would need to include at least 14 studies with a mean sample size of 50 (25 participants per condition), to be able to detect an effect size of Hedges's $g = 0.30$ (conservatively assuming a high level of between-study variance, a statistical power of 0.80, and a significance level, α , of 0.05). Alternatively, we would need 18 studies with 40 participants each to detect an effect size of Hedges's $g = 0.30$, or 24 studies with 30 participants. As we included 21 studies for the TE group (median of 16 participants, range 5–265) versus the NE group (median of 15 participants, range 8–183) and 34 studies for the TE group (median of 15, range 5–265) versus the PTSD group (median of 21 participants, range 7–75), our analyses were sufficiently powered.

A post hoc power calculation showed that the 21 studies comparing non-exposed with trauma-exposed subjects had sufficient power to detect a significant effect size of 0.16, and the 34 studies comparing PTSD with trauma-exposed subject had sufficient power to detect a significant effect size of 0.15.

Subgroup analysis

For each subgroup, the pooled mean effect size was calculated, and a test was conducted to examine putative differ-

ences in effect sizes. Subgroup analyses were conducted for the following characteristics: HPA-axis outcome measure, type of trauma, gender, age groups, and quality of the studies. For all subgroup analyses, random effects models were used.

Results

Search and inclusion

The literature search combining the key words and MeSH terms resulted in 1511 studies (Supplement 1). After the first screening of abstracts and methods sections to select studies with a TE group, an NE control group and/or a group of PTSD patients, cortisol as an outcome measure and one of the five ways to assess HPA-axis functioning (Fig. 1), 150 studies were left. These studies were requested in full-text and screened in more detail by two raters (EK and EG or TV) independently. Thirty-nine of these 150 studies were discussed in detail to reach consensus about in- or exclusion. After this second screening, another 111 studies were excluded, leaving 39 studies eligible for our meta-analyses. The main reasons for exclusion in this phase were (1) no TE group was present ($n = 45$); (2) childhood trauma and not adult trauma exposure was assessed ($n = 20$); and (3) neither a PTSD patient group or a NE control group was studied ($n = 14$) (S1). From the corresponding authors of 10 studies we requested additional information on cortisol levels and on the exclusion of (childhood) trauma exposure. From seven of these (Lauc et al., 2004; Pico-Alfonso et al., 2004; Rohleder et al., 2004; Olff et al., 2006; Wessa et al., 2006; Simeon et al., 2008; Johnson et al., 2008), we received the requested data and the studies were included in the meta-analyses. Unfortunately, three authors did not respond to our request (Boscarino, 1996; Kanter et al., 2001; Neylan et al., 2003b). As a result, two of these studies were not included, whereas for one study we could only include basal cortisol data (Neylan et al., 2003b).

Study characteristics

The characteristics of the 37 included studies are outlined in Supplement 2. A total of 2468 subjects were included (1120 TE subjects, 508 NE controls, and 840 PTSD patients). The majority of the studies ($n = 18$) included a TE, an NE and a PTSD group. In an additional 17 studies only TE subjects and PTSD patients were examined, and three studies compared TE subjects and NE controls exclusively. As a result, the meta-analysis comparing TE subjects with NE control subjects included 21 studies, whereas the meta-analysis of TE subjects and PTSD patients included 34 studies. The majority of the studies included adult subjects (18–65 years of age), whereas three studies included older adults. Twelve studies included military personnel with combat exposure and seven studies included individuals with exposure to the Holocaust (Yehuda et al., 1995b, 2005a,b, 2009), war (Rohleder et al., 2004; Roth et al., 2006) or genocide (Eckart et al., 2009). One study included both combat veterans and Holocaust survivors (Yehuda et al., 2002). One study included both combat veterans and individuals exposed to various civilian trauma (Yehuda et al., 2004b). Five studies included women with a history of violence by an intimate partner (Seedat et al.,

2003; Pico-Alfonso et al., 2004; Griffin et al., 2005; Inslicht et al., 2006; Johnson et al., 2008) and 14 studies assessed individuals with other types of trauma (e.g., motor vehicle accidents, assault, disaster).

Thirty studies assessed basal cortisol; for this, 19 used salivary samples, six studies used plasma cortisol samples, and five studies assessed 24-h urinary cortisol (Pitman and Orr, 1990; Yehuda et al., 1995b, 2009; Bierer et al., 2006; Simeon et al., 2008). Three studies assessed basal cortisol at two time points over the day (Pico-Alfonso et al., 2004; Young and Breslau, 2004; Gill et al., 2008) and seven studies assessed salivary cortisol at multiple time points (Young et al., 2004; Yehuda et al., 2005a,b; Inslicht et al., 2006; Lindauer et al., 2006; Roth et al., 2006; Eckart et al., 2009). From one study we were only able to use an AM salivary cortisol sample because additional information was not available (Neylan et al., 2003b). Of the studies of salivary cortisol, eight calculated the salivary cortisol response to awakening (CAR) (Lauc et al., 2004; Rohleder et al., 2004; Olff et al., 2006; Wessa et al., 2006; de Kloet et al., 2007; Johnson et al., 2008; Klaassens et al., 2010a,b). Of the seven studies of plasma cortisol, six sampled at one time point (Yehuda et al., 2002; Bonne et al., 2003; Neylan et al., 2003a; Seedat et al., 2003; Liberzon et al., 2007; Shalev et al., 2008) and one study collected 24-h plasma cortisol (Golier et al., 2007).

Nine studies used the low dose dexamethasone suppression test (DST) (Yehuda et al., 1995a, 2002, 2004b; Bachmann et al., 2005; Griffin et al., 2005; Golier et al., 2006; de Kloet et al., 2007; Metzger et al., 2008; Simeon et al., 2008) of which seven assessed plasma cortisol (Yehuda et al., 1995a, 2002, 2004b; Bachmann et al., 2005; Griffin et al., 2005; Golier et al., 2006; Simeon et al., 2008), one study assessed salivary cortisol (Metzger et al., 2008), and one study assessed cortisol suppression after dexamethasone both in salivary and in plasma cortisol (de Kloet et al., 2007). The majority of these studies assessed pre- and post-Dex cortisol in morning samples, whereas two studies used afternoon samples (Yehuda et al., 1995a; de Kloet et al., 2007). Two studies that assessed HPA-axis functioning with the DST also assessed the CAR (de Kloet et al., 2007; Simeon et al., 2008). Two studies assessed plasma cortisol levels after the Dex/CRH challenge test in addition to the CAR (Klaassens et al., 2010a,b).

Two of the 37 studies met all 8 quality criteria (Klaassens et al., 2010a,b), 14 studies (38%) were considered of good quality (i.e., meeting five or more criteria). All 37 studies met the criterion for detailed trauma assessment. Only four studies sampled basal cortisol on more than one day (Pico-Alfonso et al., 2004; Rohleder et al., 2004; Klaassens et al., 2010a,b). Of the 19 studies that sampled salivary cortisol, 14 gave extensive sampling instructions in order to increase compliance (Lauc et al., 2004; Pico-Alfonso et al., 2004; Young et al., 2004; Young and Breslau, 2004; Lindauer et al., 2006; Roth et al., 2006; Wessa et al., 2006; de Kloet et al., 2007; Gill et al., 2008; Johnson et al., 2008; Metzger et al., 2008; Eckart et al., 2009; Klaassens et al., 2010a,b). None of the studies used time-monitoring devices. Twenty-five studies checked for potential confounders (Yehuda et al., 2005a), adjusted for potential confounders (Yehuda et al., 2002, 2004b, 2005b, 2009; Bonne et al., 2003; Neylan et al., 2003b; Pico-Alfonso et al., 2004; Rohleder et al., 2004; Young et al., 2004; Young and Breslau, 2004; Griffin et al., 2005; Golier et al., 2006, 2007; Inslicht et al., 2006; Olff et al.,

2006; Wessa et al., 2006; de Kloet et al., 2007; Shalev et al., 2008; Gill et al., 2008; Johnson et al., 2008; Metzger et al., 2008; Klaassens et al., 2010a,b) or excluded participants on potentially confounding variables such as smoking (Eckart et al., 2009). Of the 37 included studies, 19 excluded all psychotropic medication, seven did not mention medication use (Neylan et al., 2003b; Lauc et al., 2004; Young et al., 2004; Bierer et al., 2006; Roth et al., 2006; Shalev et al., 2008; Metzger et al., 2008). Lifetime psychiatric disorders were excluded in TE and/or NE subjects in ten studies (Yehuda et al., 1995b, 2005a, 2009; Bonne et al., 2003; Neylan et al., 2003a; Seedat et al., 2003; Rohleder et al., 2004; Olff et al., 2006; Klaassens et al., 2010a,b), whereas the other 27 studies did not exclude lifetime psychiatric disorders in their TE subjects or NE controls or did not report this.

Most quality points were lost by not assessing HPA-axis functioning on more than one day and by not excluding subjects with a history of psychiatric disorders in the control groups. When we considered the quality of studies regardless of assessment on one or more days, 10 studies were of less than optimal quality. Overall, the quality of HPA-axis assessment was good to excellent, most studies adjusted their findings for confounders and all described detailed assessment of trauma exposure during adulthood. This made us decide to include these 37 studies in our meta-analyses. The median quality score of studies assessing basal cortisol levels was 4 and the median quality score of studies assessing HPA-axis reactivity with the DST was 5 and for the two studies using the Dex/CRH test (Klaassens et al., 2010a,b) the median score was 8 points.

TE subjects versus NE control subjects

Fig. 2a shows a forest plot of the effect sizes (Hedges's g) of cortisol levels in TE subjects relative to NE controls subjects in each of the 20 studies. The pooled effect size (Hedges's g) using the random-effects model was -0.029 (95%CI: -0.145 ; 0.088), which suggests no difference in basal cortisol levels between TE subjects and NE controls with adult trauma-exposure. The overall analysis was performed without the DST and Dex/CRH outcomes. There was no heterogeneity ($I^2 = 0.00\%$, $p = 0.468$) in results between studies (Table 1a).

TE subjects versus PTSD patients

Fig. 2b shows a forest plot of the effect sizes (Hedges's g) of cortisol levels in TE subjects relative to patients with PTSD in each of the 34 studies. The overall analysis was performed without the DST outcome. There was significant heterogeneity ($I^2 = 68.26\%$, $p < 0.001$) in results between studies. The pooled effect size (Hedges's g) using the random-effects model was 0.175 (95%CI: -0.012 ; 0.362), which suggests no difference in HPA axis functioning between TE subjects and PTSD patients with adulthood trauma exposure (Table 1b).

Subgroup analyses

All subgroup analyses were performed separately for the TE versus the NE subjects and for the TE subjects versus the PTSD patients.

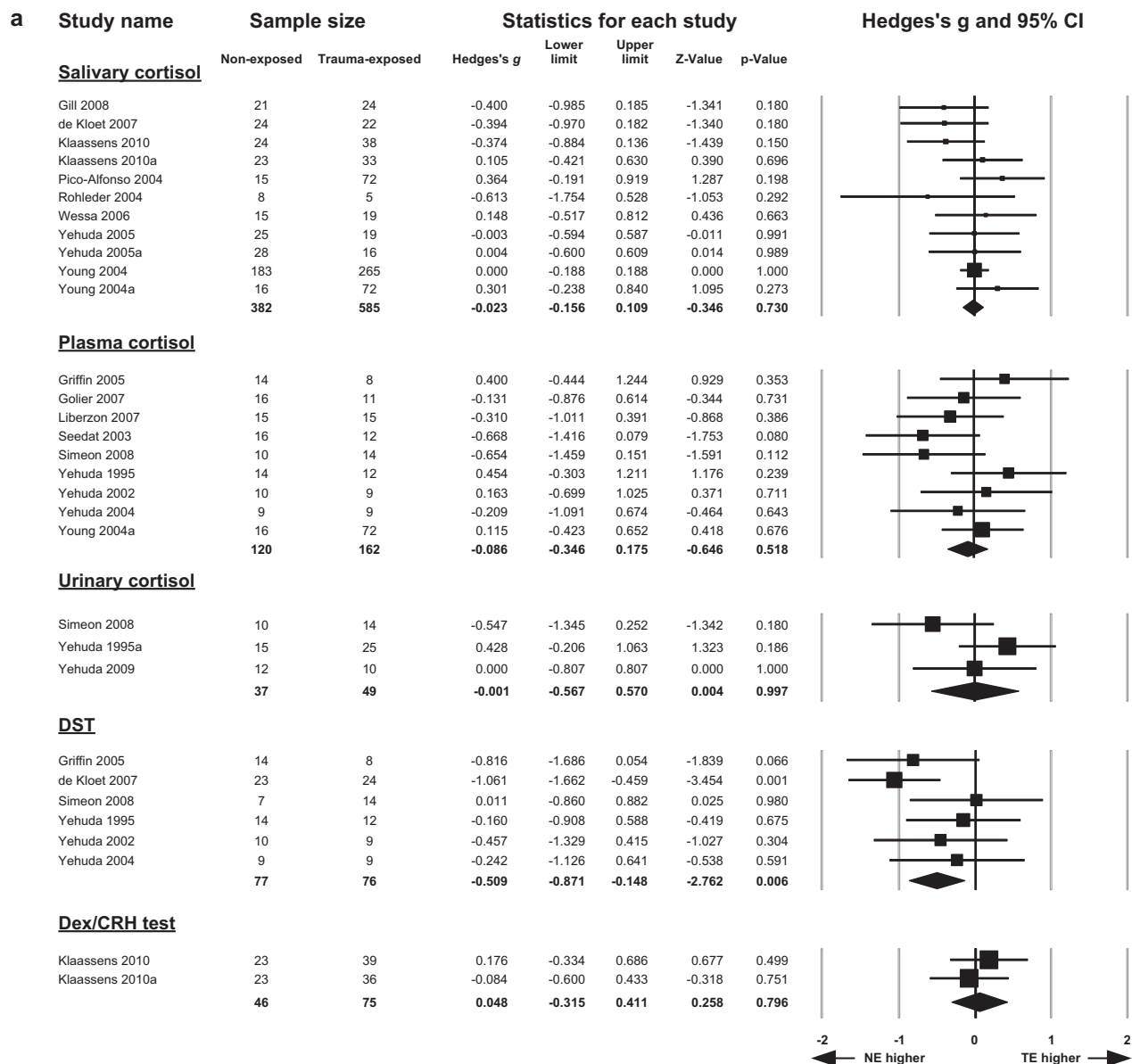


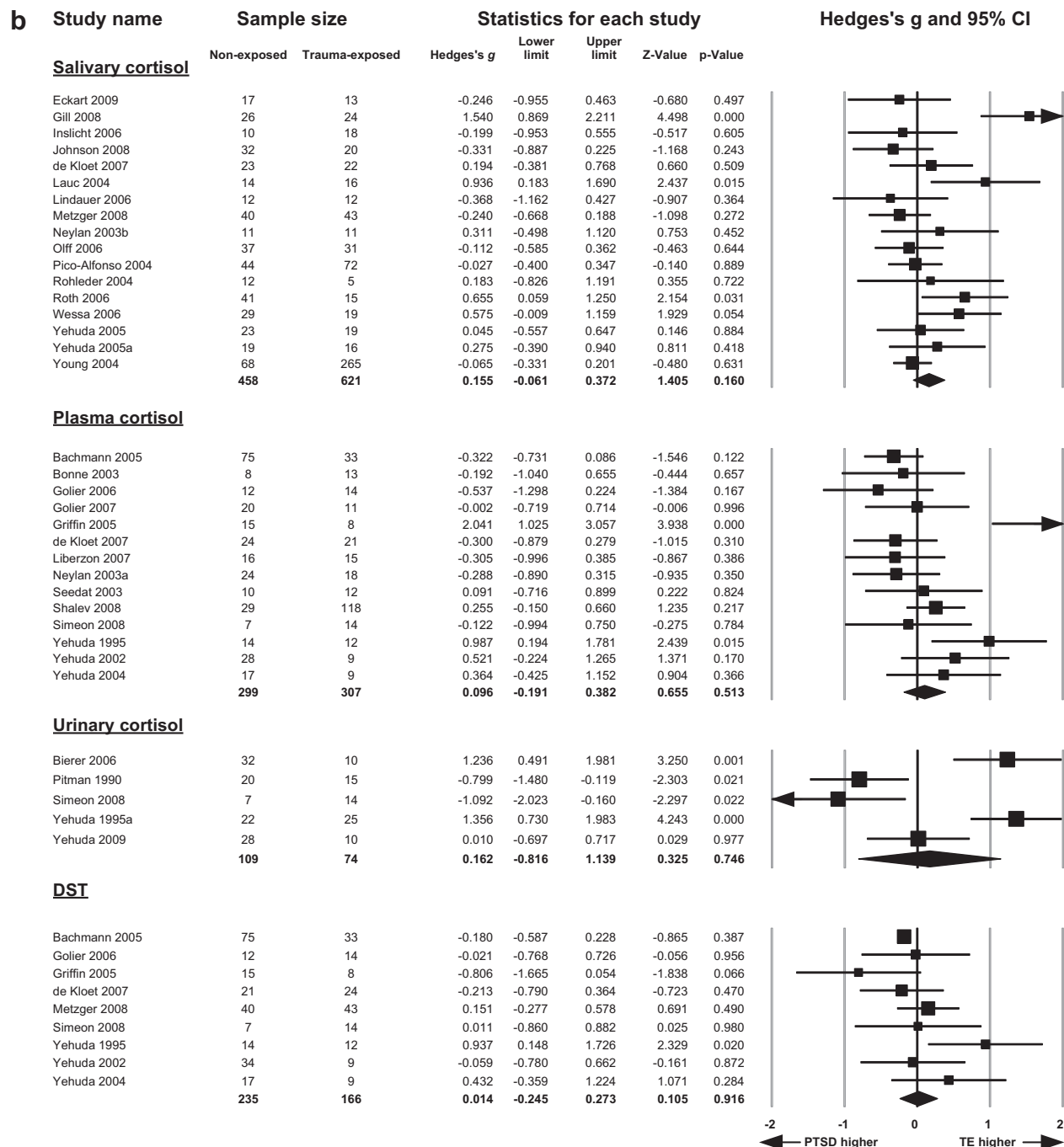
Figure 2 (a) Hedges's pooled effect sizes (with 95% confidence interval) of cortisol levels between trauma-exposed and non-trauma exposed individuals without psychiatric disorders (n = 20 studies). Pooled estimate based on random-effects model. (b) Hedges's pooled effect sizes (with 95% confidence interval) of cortisol levels between trauma-exposed individuals without psychiatric disorders and PTSD patients (n = 34 studies). Pooled estimate based on random-effects model.

In the subgroup analyses for HPA-axis outcome measure, we performed subgroup analyses for the different basal measures of cortisol (i.e., saliva, blood, and urine) as well as for the dynamic cortisol measures (DST and Dex/CRH). No differences were found in the basal outcome measures or in the Dex/CRH cortisol levels. However, in the subgroup analysis on cortisol suppression after the low dose DST, a stronger cortisol suppression in TE subjects (Hedges's $g = -0.509$, $p = 0.006$) relative to NE subjects was found (Table 1a). The pooled effect size for the DST, however, was not statistically significant when comparing TE subjects with PTSD patients (Table 1b).

The pooled Hedges's g , did not differ according to age, gender, type of trauma, lifetime psychiatric disorders in TE and/or NE subjects, and medication use or comorbid MDD in

PTSD patients, neither for TE subjects compared to NE controls nor for TE subjects compared to PTSD patients. When in sensitivity analyses the higher quality studies only were combined, the results remained similar. In detail, the 10 high-quality studies that compared TE versus NE yielded a Hedges's g of -0.101 and the 11 high-quality studies that compared TE versus PTSD yielded a Hedges's g of 0.169 , that were largely of strengths similar to the overall effect sizes of -0.029 and 0.175 , respectively (Tables 1a and 1b).

A post hoc sensitivity analysis in the TE versus PTSD groups revealed that the 5 studies with Holocaust victims showed the largest effect size that approached statistical significance (Hedges's g 0.446 , $p = 0.084$), followed by the 18 studies that included other forms of trauma (Hedges's g 0.237 , $p = 0.077$), while no hint for an effect was found in



studies on trauma experienced during combat (Hedges's $g = -0.044$, $p = 0.770$; Table 1b).

There were no significant interactions between, on the one hand, TE versus NE and TE versus PTSD, and, on the other hand, subgroups (all $ps > 0.20$ for interaction). In other words, subgroups did not significantly differ for their effect sizes, in none of the meta-analyses.

In the two main analyses, neither the funnel plot nor Duval and Tweedie's trim and fill procedure pointed at a significant publication bias (data not shown). The effect sizes did not change after adjustment for possible publication bias in both analyses (the observed and adjusted effect sizes were

exactly the same, and the number of imputed studies was zero).

Discussion

Our main finding is that TE individuals in the absence of psychopathology did not differ on basal cortisol levels from NE healthy control subjects. Moreover, PTSD patients did not differ from TE subjects with respect to basal cortisol levels. Results were largely consistent for saliva, plasma and urine in which the cortisol was measured. The only significant differ-

Table 1a Meta-analysis of studies examining the effects of adult trauma exposure versus control subjects not exposed trauma on HPA-axis regulation.

Comparison	Number of studies	Number of subjects per group TE/NE	Hedges's g	95%CI	p-Value for effect size	Z	Q	I ²	p-Value for heterogeneity
<i>Trauma-exposed (TE) and non-exposed (NE) healthy subjects</i>									
All studies (without DST and Dex/CRH)	21	710/513	−0.029	−0.146; 0.087	0.620	−0.495	19.636	0.00	0.481
Outcome									
Salivary cortisol	11	585/382	−0.023	−0.156; 0.109	0.730	−0.346	9.852	0.00	0.454
Plasma cortisol	9	162/120	−0.089	−0.345; 0.168	0.498	−0.678	8.581	6.77	0.397
Urinary cortisol	3	49/37	−0.001	−0.567; 0.570	0.997	−0.004	3.521	43.20	0.172
DST	6	76/77	−0.482	−0.862; −0.102	0.013	−2.484	6.901	27.55	0.228
Dex/CRH test	2	75/46	0.048	−0.315; 0.411	0.796	0.258	0.492	0.00	0.483
Type of trauma									
Combat	5	93/92	−0.077	−0.363; 0.209	0.599	−0.526	3.732	0.00	0.444
Holocaust	5	79/90	0.117	−0.185; 0.419	0.447	0.761	1.309	0.00	0.860
Other	11	538/331	−0.085	−0.285; 0.115	0.405	−0.832	13.504	25.95	0.197
Gender									
Male	5	120/100	−0.146	−0.436; 0.144	0.324	−0.986	4.723	15.23	0.317
Female	5	188/82	0.001	−0.408; 0.410	0.998	0.003	8.229	51.39	0.084
Age									
≤40 years	8	413/288	−0.097	−0.310; 0.116	0.374	−0.889	8.563	18.26	0.286
>40 years	13	297/225	−0.007	−0.172; 0.185	0.942	−0.072	10.801	0.00	0.546
Quality									
High	10	299/171	−0.101	−0.330; 0.128	0.388	−0.863	11.685	22.98	0.232
Suboptimal	11	411/342	−0.005	−0.138; 0.149	0.941	0.074	7.302	0.00	0.697

Note: HPA-axis, hypothalamus–pituitary–adrenal-axis; TE, trauma exposed healthy subjects; NE, non-exposed healthy subjects; 95%CI indicates 95% confidence interval; DST, dexamethasone suppression test; Dex/CRH, dexamethasone corticotropin-releasing hormone.

Table 1b Meta-analysis of studies examining the effects of trauma exposure versus PTSD on HPA-axis regulation.

Comparison	Number of studies	Number of subjects per group TE/PTSD	Hedges's <i>g</i>	95%CI	<i>p</i> -Value for effect size	<i>Z</i>	<i>Q</i>	<i>I</i> ²	<i>p</i> -Value for heterogeneity
<i>Trauma-exposed (TE) healthy subjects and PTSD patients (PTSD)</i>									
All studies (without DST)	34	967/835	0.177	−0.011; 0.365	0.065	1.846	104.842	68.52	0.000
Outcome									
Salivary cortisol	17	621/458	0.155	−0.061; 0.372	0.160	1.405	39.217	59.20	0.001
Plasma cortisol	14	307/299	0.102	−0.188; 0.393	0.491	0.689	33.752	61.48	0.001
Urinary cortisol	5	74/109	0.162	−0.816; 1.139	0.746	0.325	36.213	89.95	0.000
DST	9	166/236	−0.009	−0.272; 0.255	0.949	−0.064	12.144	34.12	0.145
Type of trauma									
Combat	11	210/269	−0.044	−0.343; 0.254	0.770	−0.292	24.806	59.69	0.006
Holocaust	5	79/120	0.446	−0.060; 0.952	0.084	1.726	11.561	65.40	0.021
Other	18	678/446	0.237	−0.026; 0.499	0.077	1.768	11.561	65.40	0.021
Gender									
Male	10	169/226	−0.034	−0.377; 0.310	0.847	−0.192	24.588	63.40	0.003
Female	7	197/177	0.341	−0.222; 0.904	0.235	1.188	37.475	83.99	0.000
Age									
≤40 years	13	538/274	0.103	−0.166; 0.372	0.452	0.752	28.499	57.89	0.005
>40 years	21	429/561	0.220	−0.042; 0.483	0.100	1.645	75.578	73.54	0.000
Quality									
High	11	227/221	0.169	−0.235; 0.573	0.412	0.820	39.468	74.66	0.000
Suboptimal	22	731/586	0.169	−0.051; 0.389	0.133	1.504	64.152	67.27	0.000

Note: HPA-axis, hypothalamus–pituitary–adrenal-axis; TE, trauma exposed subjects; PTSD, posttraumatic stress disorder patients; 95%CI indicates 95% confidence interval; DST, dexamethasone suppression test; Dex/CRH, dexamethasone corticotropin-releasing hormone.

ence concerned DST findings, as adulthood trauma may augment cortisol suppression after the DST. As mentioned earlier, in trauma-exposed veterans without PTSD enhanced suppression of cortisol is reported (de Kloet et al., 2007). This is in line with pre-clinical studies that showed long-term alteration in glucocorticoid regulation in response to an acute or chronic stressor (van Dijken et al., 1993; Buwalda et al., 1999). Increased sensitivity of the HPA-axis to corticosteroids after trauma exposure may be a mechanism of the body to protect itself against the detrimental effects of sustained high cortisol levels.

In contrast to exposure to childhood trauma, which is associated with alterations in HPA-axis functioning (Heim et al., 2000; Rinne et al., 2002; Meinschmidt and Heim, 2005; Carpenter et al., 2007; Tyrka et al., 2008; Klaassens et al., 2009), trauma during adulthood was not associated with basal cortisol. This is also in line with our post hoc sensitivity analysis in which we excluded Holocaust studies, which markedly attenuated the effect size. This seems valid as trauma exposure during the Holocaust very likely also included trauma exposure during childhood. At least some of the Holocaust survivors that were included were likely to be under 16 years of age when they were subjected to a life in a concentration camp, ghetto or in hiding, and therefore the tendency for a stronger effect size may have been due to the fact that part of the subjects were exposed to trauma during childhood rather than adulthood."

Our main finding of a lack of association, is also in line with a subgroup analysis from the meta-analysis of Meewisse et al. (2007) on basal cortisol in adult subjects with and without PTSD, as they found no differences between people with PTSD and TE controls. In our meta-analysis, however, we extended the analysis from 15 studies that were included in their meta-analysis (Meewisse et al., 2007) to 34 studies in ours. Moreover, we exclusively focussed on adulthood trauma, whereas the other meta-analysis also included studies on victims of childhood sexual and physical abuse. Thus, our meta-analysis lends support for the hypothesis that *adulthood* trauma does not (markedly) affect HPA-axis functioning.

We included the dynamic DST and the Dex/CRH test in our meta-analyses, contrary to the former meta-analysis (Meewisse et al., 2007). Our analysis suggested that studies using the DST found more cortisol suppression in TE subjects compared with NE controls. Trauma-exposure during adulthood may thus be associated with a stronger HPA-axis feedback response. This suggests that the often-reported association between PTSD and negative feedback systems of cortisol could be trauma-related. Our second meta-analysis, however, did not extend this finding to PTSD subjects; no differences in effect size on the DST were found between TE subjects and PTSD patients. Differences in HPA-axis functioning between these groups have been ascribed to the presence of PTSD. In light of our findings, however, DST differences could be associated with trauma exposure rather than with PTSD psychopathology. Yet, the findings on the DST in TE versus NE subjects, were based on only 5 studies, and should be interpreted cautiously. Based on only two studies, no association was found between trauma exposure in adulthood and HPA-axis functioning during the Dex/CRH challenge test (Klaassens et al., 2010a,b).

There are several possible explanations for the inconsistent findings in previous studies when comparing PTSD

patients to NE participants. First, the PTSD group may consist of a heterogeneous patient groups, as different forms of adult trauma (e.g., sexual violence/abuse, combat, Holocaust) were studied in different publications. Second, non-linear associations with cortisol could exist that was not investigated with the techniques used in our meta-analysis. Recent publications showed both hypo- and hyperactivity of the HPA-axis being associated with depression (Bremmer et al., 2007; Penninx et al., 2011) or its dimensions in subjects with and without anxiety and depressive disorders (Wardenaar et al., 2011), which might also be present in PTSD. Third, publication bias may play a role, even if no true difference is present between the two groups. Studies finding either significantly enhanced or diminished cortisol levels in PTSD (Type 1 errors) may have higher chances to be published than studies that showed non-significant results. This may also explain the larger heterogeneity between study results when comparing TE versus PTSD subjects."

Limitations and strengths

The results of this meta-analysis should be interpreted in light of the limitations of the analyses and the body of studies within it. First, despite our efforts to include all available studies and good agreement between the reviewing authors, we cannot rule out the possibility that we have missed some studies meeting the inclusion criteria and we could not calculate inter-rater reliability scores for double-screening scores from pairs of reviewing authors. Fortunately, publication bias analyses suggest that, although some studies may have been missed, publication bias is unlikely to have influenced our findings. Second, in the process of designing these meta-analyses, several decisions based on our in- and exclusion criteria were made. Different criteria might have led to slightly different results. Third, we have included studies that did not specifically mention the assessment of childhood trauma exposure. We have taken the shortcoming of these studies into account in the quality score, which was used to do a sensitivity analysis only in studies of higher quality (Tables 1a and 1b). Fourth, not all studies explicitly stated whether they assessed lifetime psychiatric illness using (semi-)structured interviews, and therefore may have included subjects with past diagnoses of, e.g., adjustment disorders, mood disorders, and acute stress disorder. Fifth, some of the included studies had very small sample sizes, mostly as a result of the fact that the two control groups (TE and NE) were initially recruited as one control group and subgroup analyses were later performed. Finally, the quality of most studies (59%) was not optimal. Some studies assessed only one basal sample of cortisol, which in most cases was not related to time of awakening. The cortisol level assessed with a single time-point sample is very easily influenced by stress (e.g., in case of a vena puncture) or daytime variability. A strength of our meta-analysis was that we did not only include studies on basal cortisol sampling but also studies of cortisol reactivity to the DST and the Dex/CRH challenge test. In doing so, we have tried to create a more complete picture of HPA-axis functioning in relation to exposure to adulthood trauma in subjects with and without psychiatric disorders.

Conclusion

The lack of difference in pooled effect size between subjects with and without adult trauma exposure suggests that trauma exposure during adulthood per se is unlikely to affect basal HPA-axis functioning in subjects without PTSD. In addition, no evidence was found for an association of PTSD with basal HPA-axis functioning. Moreover, the lack of heterogeneity for the first meta-analysis suggests that additional studies on trauma exposure during adulthood are unlikely to yield different results. Interestingly, in a subgroup analysis of 5 studies we found that in the DST there was more cortisol suppression in TE subjects than in NE controls.

There are some (clinical) implications of our findings. Since there seems to be an interaction between trauma exposure, HPA-axis regulation and stress-related disorders such as PTSD, this may help us understand why some people do and others do not develop psychiatric disorders in the aftermath of traumatic stress. Moreover, the enhanced suppression after the DST may be contributing to an increased vulnerability to further exposure to stressors in the trauma-exposed subjects. Nevertheless, as we did not find large differences in basal cortisol levels among the groups, we advice further studies in this field to focus on more sensitive dynamic tests of HPA-axis integrity. In future studies on the effects of trauma, not only in patients with PTSD but also in patients with other psychiatric disorders, we therefore propose to carefully differentiate between adulthood and childhood trauma. Moreover, as most data is present for basal cortisol and the low-dose DST, more evidence on other dynamic tests of HPA-axis functioning in PTSD and adulthood trauma exposure is needed (e.g., de Kloet et al., 2008).

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.psyneuen.2011.07.003](https://doi.org/10.1016/j.psyneuen.2011.07.003).

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